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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,425	03/03/2005	Tsuneko Okazaki	80161(302730)	9673
21874	7590	02/17/2009	EXAMINER	
EDWARDS ANGELL PALMER & DODGE LLP			HILL, KEVIN KAI	
P.O. BOX 55874			ART UNIT	PAPER NUMBER
BOSTON, MA 02205			1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/526,425	Applicant(s) OKAZAKI ET AL.
	Examiner KEVIN K. HILL	Art Unit 1633

—The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

THE REPLY FILED 13 January 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) The period for reply expires 5 months from the mailing date of the final rejection.
- b) The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because

- (a) They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) They raise the issue of new matter (see NOTE below);
- (c) They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet. (See 37 CFR 1.116 and 41.33(a)).

4. The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. Applicant's reply has overcome the following rejection(s): _____.

6. Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. For purposes of appeal, the proposed amendment(s): a) will not be entered, or b) will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: 1, 4-7, 13-14.

Claim(s) withdrawn from consideration: _____

AFFIDAVIT OR OTHER EVIDENCE

8. The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fail to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

12. Note the attached *Information Disclosure Statement(s)*. (PTO/SB/08) Paper No(s). _____

13. Other: _____

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Continuation of 3. NOTE: The proposed amendment(s) to the claims add new limitations, thereby raising new issues which would require further search and consideration, e.g. introducing into a first mammalian host cell a first vector and introducing into a second host cell a second vector, if the proposed amendment was entered.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 4-6 and 13-14 stand rejected for reasons of record in the Office Action mailed August 14, 2008. Applicant requests reconsideration after final Office Action.

Claims 1, 4-6 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mejia et al in further view of Waye et al, Ikeno et al and Perkins et al.

Response to Arguments

Applicant argues that:

- a) Mejia does not teach a second vector that comprises an insertion sequence and an insulator sequence,
- b) Mejia does not teach the method being performed in mammalian cells,
- c) Perkins does not teach insertion sequences which is a loxP site or a FRT site,
- d) the combination of references fail to teach the claimed insertion sequence or insulation sequence, and
- e) the MAC of the instant invention has an insulator sequence for the purpose of promoting the expression of a gene to be introduced later, and it was found by the inventors that, surprisingly, both the efficiency of gene transfer into the mammalian artificial chromosome and the efficiency of the expression of the gene were enhanced.

Applicant's arguments have been fully considered, but are unpersuasive.

With respect to a-c), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Applicant appears to have overlooked that Mejia teaches a second vector being in circular form and comprising an insertion sequence for specifically inserting a sequence of interest, wherein the insertion sequence is a loxP recombination site, and that Perkins successfully demonstrated methods of producing artificial chromosomes in mammalian cells.

With respect to d), human alpha satellite insulator sequences comprising nucleic acid sequences 100% identical to SEQ ID NO:1 were known in the prior art. Thus, it is unclear how the combination of the cited references fail to teach the claimed insertion sequence (discussed immediately above) or insulation sequence.

With respect to e), as a first matter, the claims are drawn to a method of making a mammalian artificial chromosome, not a method of enhancing gene expression in a mammalian artificial chromosome. As a second matter, the insulator activities found by Applicant necessarily flow from the insulator elements, and thus would necessarily be present and achieved by the insulator elements taught in the prior art and structurally indistinguishable from the instantly claimed insulator element.

Claims 1 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mejia et al, in further view of Waye et al, Ikeno et al and Perkins et al, as applied to claims 1, 4-6 and 13 above, and in further view of Bokkelen et al.

Response to Arguments

Applicant argues that Bokkelen et al do not cure the flaws of Mejia et al, Waye et al, Ikeno et al and Perkins et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to the arguments regarding the combination of Mejia et al, Waye et al, Ikeno et al and Perkins et al discussed above are incorporated herein. Applicant does not contest the teachings of Bokkelen et al as applied to the obviousness to substitute the mammalian centromere sequence length of Mejia et al with a mammalian centromere sequence length of about 50kb or less as taught be Bokkelen et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims 1 and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mejia et al, in further view of Waye et al, Ikeno et al, Perkins et al and Bokkelen et al, as applied to claims 1, 4-7 and 13 above, and in further view of Cooke et al.

Response to Arguments

Applicant argues that Bokkelen et al do not cure the flaws of Mejia et al, Waye et al, Ikeno et al, Perkins et al and Bokkelen et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to the arguments regarding the combination of Mejia et al, Waye et al, Ikeno et al, Perkins et al and Bokkelen et al discussed above are incorporated herein. Applicant does not contest the teachings of Cooke et al as applied to the obviousness to try adjusting the molecular ratio of the first and second vector in a cloning reaction to be in the range from about 10:1 to about 1:10 molecular ratio because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." Adjusting the relative ratios between a first (donor) nucleic acid and a second (target) nucleic acid in a molecular cloning reaction has long been practiced in the art.